TEST PLAN FOR N-(METHYL)-ACRYLAMIDES CATEGORY

7 September 2001

OVERVIEW

The NMA/NBMA Association hereby submits for review a test plan for a category consisting of two substituted N-(methyl)-acrylamides under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of the panel and its member companies to use existing data on these two compounds and data available on a very closely related chemical, acrylamide, to adequately fulfill the Screening Information Set (SIDS) for environmental fate endpoints, ecotoxicity tests, and human health effects for the two substituted N-(methyl)-acrylamides. The NMA/NBMA Association believes that adequate data exist to fulfill all the requirements of the HPV program without the need for additional testing.

Test Plan Matrix for N-(Methyl)-Acrylamides

Chemical	Acrylamide (AMD) CAS # 79-06-1	N-(hydroxymethyl) NMA CAS # 924-42-5	N-(butoxymethyl) NBMA CAS # 1852-16-0
PHYSICAL CHEMISTRY			
Melting Point	Y,E	Y,E	E
Boiling Point	Y	Y,E	Y,E
Vapor Pressure	Y	Y,E	E
Water Solubility	Y	Y,E	Y,E
Pow (Kow)	Y	E	E
ENVIRONMENTAL FATE			
Photodegradation	Y,E	E	E
Stability in Water	Y,E	Y,E	E
Biodegradation	Y	Y,E	Y,E
Transport between Environmental Compartments (Fugacity)	E	E	E
ECOTOXICITY			
Acute Toxicity to Fish	Y	Y	Y
Acute Toxicity to Aquatic Invertebrates	Y	C	C
Toxicity to Aquatic Plants	Y	C	C
Toxicity to Avian Species	Y	NR	NR
TOXICOLOGICAL DATA			
Acute Toxicity	Y	Y	Y
Repeated Dose Toxicity	Y	Y	Y
Genetic Toxicity-Mutation	Y	Y	Y
Genetic Toxicity-Chromosomal Aberrations	Y	Y	Y
Carcinogenicity	Y	Y	C
Toxicity to Reproduction	Y	Y	C
Developmental Toxicity	Y	C	C
OTHER TOXICITY DATA			
Human Experience	Y	NR	NR
Pharmacokinetics	Y	Y	NR

Y = Adequate experimental data
E = Endpoint fulfilled via EPIWIN model.
C = Endpoint fulfilled by category approach
NA = Not applicable
NR = Not required

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1. Information about the Panel

The NMA/NBMA Association consists of the following manufacturers:

Cytec Industries Inc. 5 Garret Mountain Plaza West Paterson, NJ 07424	National Starch (ICI) 10 Finderne Avenue Bridgewater, NJ 008807

2. Category Analysis

2.1 Identity of Category Members

The substances included in the substituted acrylamide category are as follows:

2.1.1 Acrylamide, N-(hydroxylmethyl)-,. N-Methylolpropenamide, or N-Methylolacrylamide Acrylamide, N-(hydroxylmethyl) CAS No. 924-42-5
Designated as “NMA.”

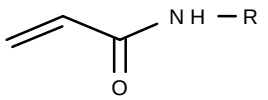
2.1.2 Acrylamide, N-(butoxymethyl)-, N-Methylolpropenamide or N-Methylolacrylamide CAS No. 1852-16-0
Designated as “NBMA.”

2.1.3 The above two compounds will be supported in part by information available for Propenamide or Acrylamide CAS No. 79-06-1
Designated as “AMD.”

2.2 Background Information on Category Members

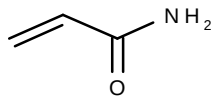
2.2.1 NMA/NBMA is a precursor monomer for manufacturing polymers, which are used in a variety of commercial applications. The monomer is produced using closed system technology. It is then transported to production sites of choice to be converted into polymers. These reactions also use closed system technology.

2.2.2 The three substances identified above (AMD, NMA, and NBMA) can be grouped together because of their close structural similarities and relatively minor structural differences. The similarity is based upon the fact that the structure of all three substances contains the “propenamide” or the “acrylamide” moiety. The generic molecular structure of all category members is shown below:

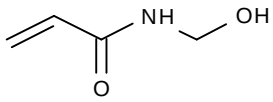


R = H, -CH$_2$OH or -CH$_2$OCH$_2$CH$_2$CH$_2$CH$_3$

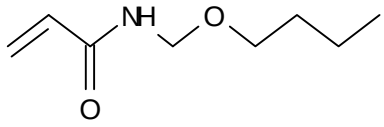
2.2.3 The structural difference between these three compounds results from a substitution on acrylamide to form the other two compounds. Thus, when one of the hydrogens on the nitrogen atom is replaced with either methylol (-CH2OH) or butoxymethyl (-CH2OCH2CH2CH2CH3) group, NMA or NBMA are formed, respectively.



AMD



NMA



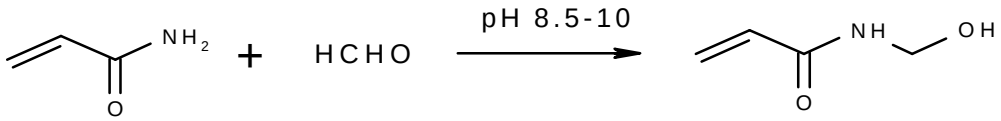
NBMA

2.3 Chemical Reactivity and Metabolism

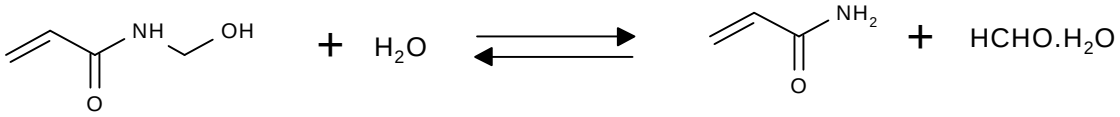
Acrylamide is a crystalline solid, which is chemically stable at room temperature. Aqueous solutions of acrylamide are generally stable at room temperature. However, in the presence of free radicals it undergoes polymerization. Therefore, inhibitors are added to aqueous solutions to stabilize acrylamide.

Aqueous solutions of acrylamide hydrolyze in the presence of strong acids or strong bases.

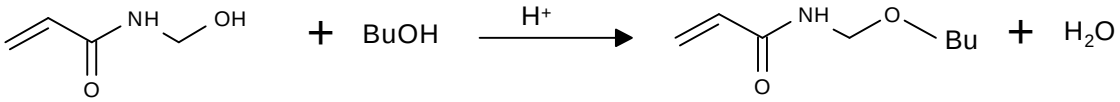
NMA is derived from acrylamide by reaction with formaldehyde at alkaline pH.



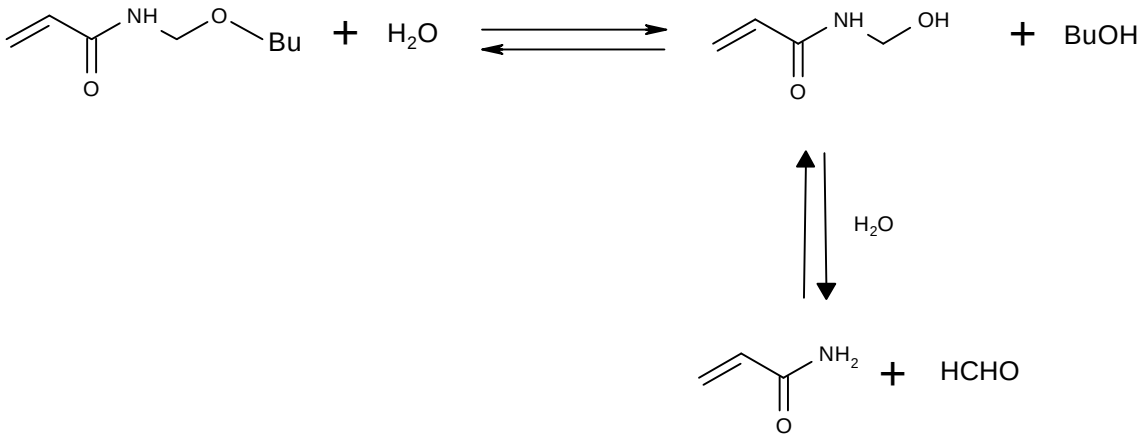
Dilute aqueous solutions of NMA are unstable at neutral pH conditions and undergo de-methylolation to acrylamide and formalin.



Alkylation of NMA with butanol under acidic conditions yields NBMA as shown. The reaction is driven to the right by employing a large excess of butanol and by removing the by-product water.



Dilute aqueous solutions of NBMA undergo hydrolysis slowly to give a mixture of NMA, AMD and formaldehyde.



3. Test Plan

As part of this HPV submission, the Agency will find three sections containing robust summaries of data related to the three chemicals (AMD, NMA and NBMA) which are the basis of this submission. The data are provided in the IUCLID format as suggested by the Agency. The following test plan summarizes those studies that the submitter believes provide the most significant information. It is not the intent of the test plan to refer to all studies listed in the data sets. However, summaries of additional studies not employed in the test plan are available to the reviewer in the data summaries.

3.1 Chemical and Physical Properties

Chemical/physical properties are summarized in Table 1.

Table 1. Chemical/physical properties of AMD, NMA, and NBMA

Endpoint	AMD (CAS # 79-06-1)	NMA (CAS # 924-42-5)	NBMA (CAS # 1852-16-0)
Melting point	*83.75 °C ** 84.5° ± 0.3 °C	*69.5 °C ** 74-75 °C	*79.9 °C **
Boiling point	87 °C @ 2.03mmHg 103 °C@ 5.03mmHg 116 °C@ 10.5mmHg 136 °C@ 24.8mmHg	*276.5 ° C ** 100 °C ***	*296.53 ° C ** 118-143 °C **
Vapor pressure	0.007mmHg @ 25°C 0.033mmHg @ 40°C 0.08mmHg @ 50°C	*0.00023mmHg @ 25 °C ** 23.76mmHg @ 25 °C ***	*0.000704mmHg @ 25 °C **
Partition coefficient (Log Pow or Kow)	-0.9	*-1.81**	*.92**
Water solubility	2155 g/l at 30° C 4260 g/l at 50° C	1,220 g/l @ 10° C 1,880 g/l @ 20° C 3,540 g/l @ 40° C 7,550 g/l @ 60° C	0.00012 mg/l @ 25°C*

* Values obtained by EPIWIN
** Values obtained using a 50% solution in butanol
*** Values obtained using a 48% aqueous solution

3.1.1 Melting Point

Melting point determinations by modeling (Klimisch et al., 1997; Syracuse Research Corporation 1998) suggest that all these compounds have moderate melting points (70° C - 85° C). Experimental studies in AMD (Van der Burg 1922, Kirk-Othmer 1991, Carpenter and Davis 1957, The Merck Index, 12th Ed.) and NMA (Feurr and Lynch 1953) confirm the accuracy of the modeling predictions.

3.1.2 Boiling Point

Information obtained on the boiling points of these three compounds suggests the boiling points are relatively similar with a slight increase with increasing structural substitution of acrylamide. These conclusions are based upon information derived from both modeling (NMA and NBMA: Klimisch et al., 1997; Syracuse Research Corporation 1998) and experimentation (experimental studies: AMD: Kirk-Othmer 1991 and The Merck Index, 12th Ed.; NMA - Cytec MSDS No. 05741; NBMA: Cytec MSDS No. 4500).

3.1.3 Vapor Pressure

The vapor pressures of all three compounds are negligible. This conclusion is based upon information derived from modeling (NMA and NBMA: Klimisch et al., 1997; Syracuse Research Corporation 1998) and experimentation (AMD: Kirk-Othmer 1991, Dow 1989, MacWilliams 1978, Thomas 1964, Carpenter and Davis 1957, and Lewis 2000; NMA: Cytec MSDS No. 05741).

3.1.4 Octanol/Water Partition Coefficients

The log Pow (Kow) values have been estimated using the EPIWIN program algorithms (NMA and NBMA: Klimisch et al., 1997; Syracuse Research Corporation 1998) and laboratory experiments (AMD: US EPA 1980, Fujisawa and Masher 1981, Hermens and Leeuwangh 1982, Lipnick et al., 1987, and Hansch and Leo 1979).

3.1.5 Water Solubility

Information on the solubility of these compounds comes from both modeling studies (NMA and NBMA: Klimisch et al., 1997; Syracuse Research Corporation 1998) and laboratory experiments. While AMD is readily soluble in water (Budavari 1989, The Merck Index, 12th Ed., Thomas 1964, and Carpenter and Davis 1957), as is also the case for NMA (Cytec Industries, Inc. 1995), the substitution employed to obtain NBMA render this compound practically insoluble (Cytec MSDS No. 4500).

3.1.6 Test Plan for Physical Properties

Pertinent physical property values have been determined either through measurement or estimations using models, such as EPIWIN. No additional determinations are needed.

3.2 Environmental Fate and Pathways

Results of environmental fate studies with AMD, NMA and NBMA are summarized in Table 2.

Table 2. Results of environmental fate studies with AMD, NMA and NBMA

Endpoint	AMD, (CAS # 79-06-1)	NMA, (CAS # 924-42-5)	NBMA, (CAS # 1852-16-0)
Photolysis (Atmospheric $T_{1/2}$)	*11.455 hours** 6.6 hours	*4.544 hours**	*2.55 hours**
Photolysis (Hydroxyl Radical Rate Constant)	*11.21 E-12 cm^3/molecule-sec** 3.83 x 10^{-12}	*28.25 E-12 cm^3/molecule-sec**	*50.41 E-12 cm^3/molecule-sec**
Stability in Water Hydrolysis	*$t_{½}$>1 yr. *(neutral pH)* Alkaline pH: -1.47 x 10^{-4}/mole/sec (55ºC) Acid pH: -1.48 x 10^{-4}/mole/sec (80ºC)	*$t_{½}$>* 1 yr. *(neutral pH)*	*$T_{½}$>1 yr. *(neutral pH)*
Biodegradation In water In Soil	*Biodegrades fast* * 100% after 6-15 days At 3 days, degradation ranged from 11 – 71% (depending upon soil type) At 14-days, degradation ranged from 74-94%. After 21-days under waterlogged conditions, degradation ranged from 76-93%.	*Biodegrades fast* * 51.9% after 28 days (Closed bottle)	*Biodegrades fast* * 79.6% after 28 days (Closed bottle)
Koc	*10.5**	*1**	*17.6**
Henry's Law Constant	*1E-009 atm-m^3/mole** 3.2x10-10	*9.45E-012 atm-m^3/mole**	*7.08E-009 atm-m^3/mole**

* Values are derived from EPIWIN model

3.2.1 Photodegradation

The results of EPIWIN modeling (Table 2) indicate that degradation accelerates with increasing substituent substitution (Klimisch et al., 1997; Syracuse Research Corporation 1998). Experimental data substantiate this conclusion (AMD: GEMS 1986, Anbar and Neta 1967, and Matthews and Sangster 1965).

3.2.2 Stability in Water

The EPIWIN model predicts that these compounds are stable in water (i.e. resistant to hydrolysis) with half- lives estimated at greater than one year (Table 2). This is substantiated by experimental results on AMD (Brown et al., 1980; Jung et al., 1980). Data is also available for a wide variety of pH's in an aqueous environment (Moens and Smets, 1957).

3.2.3 Biodegradation

The conclusion reached by modeling studies indicates that all three compounds will biodegrade rapidly in water (Klimisch et al., 1997; Syracuse Research Corporation 1998). Experimentally derived data support this conclusion (AMD: USTC 1991, Birdie et al., 1979, Winter and Wolff 1982, Brown et al., 1982, Lande et al., 1979, Yamada et al., 1979, Brown et al., 1980b, Arai et al., 1981, Dow 1975, Brown et al., 1980c, Batchelder 1975, and Croll et al., 1974; NMA and NBMA: Wang, 1991). The results in water are consistent with evidence that AMD rapidly degrades in soils under various conditions (Abdelmagid and Tabatabai, 1982)

3.2.4 Fugacity

Estimation of relative distribution of a chemical released into various environmental compartments can be estimate using the Mackay Level III fugacity model (Klimisch et al., 1997; Syracuse Research Corporation 1998*).* This model cannot be employed to predict actual environmental concentrations. One of the key assumptions underlying this model, is the assumption of zero loss of material through degradation or dispersion out of the environmental system. When applied to AMD, NMA and NBMA, the model predicts that all three compounds partition primarily to soil and to a slightly lesser degree to water. Partition to sediment and air is negligible (Table 3).

Table 3. MacKay Level III fugacity model

Medium	AMD, (CAS # 79-06-1)	NMA, (CAS # 924-42-5)	NBMA, (CAS# 1852-16-0)
	Concentration %	Concentration %	Concentration %
Air	0.032	0.000307	0.177
Water	45.3	45.3	44.5
Soil	54.3	54.6	55.3
Sediment	0.07571	0.0755	0.0794

3.2.5 New Testing Required

All endpoints have been met by experimentation or use of EPIWIN. No further testing is required.

3.3 Ecotoxicity

Results of ecotoxicity studies with AMD, NMA and NBMA are summarized in Table 4.

Table 4. Results of Ecotoxicity Studies with AMD, NMA, and NBMA

Endpoint	AMD, (CAS # 79-06-1)	NMA, (CAS # 924-42-5)	NBMA, (CAS# 1852-16-0)
Acute toxicity to fish	96 hr LC_{50} (rainbow trout) = 162 mg/l 96 hr. (rainbow trout), flow-thru, LC_{50} 110 mg/l 96 hr. LC_{50} (bluegill) 100 mg/l	96 hr LC_{50} (rainbow trout) 890 ppm NOEC 625 ppm	96 hr LC_{50} (rainbow trout) = 75 ppm NOEC <62.5 ppm
Chronic toxicity to fish	7 day LC_{50} (*carassius auratus*) 100 ppm 30day NOEC (ibid.) 50 ppm 14 day LC_{50} (*poecilia reticulata*) 2.69 and 5.78 umol/l(expt.and calc) 15 day EC_{100} (rainbow) 50 mg/l	ND	ND
Acute toxicity to Daphnia	48 hr EC_{50} = 160 mg/l	ND	ND
Chronic toxicity to crustacea	96 hr. NOEC 2.04 mg/l 28 day NOEC 2.04 (mortality) and >4.4 mg/l	ND	ND
Toxicity to algae	72 hr. EC_{50} 33.8 mg/l NOEC 16 mg/l	ND	ND
Phytotoxicity	*Imatiens sultanii* NOEC $\leq$2,000ppm *Brassuca rapa* EC_{50} 220 mg/l *Lactuca sativa* LOEC 5 ppm	ND	ND
Bioconcentration Factor (BCF)	0.86 carcass and 1.12 viscera (Fingerling trout)	Expected to be the same as AMD due to similarities in Kow	Expected to be the same as AMD due to similarities in Kow
Toxicity to birds	LD_{50} 194-236 mg/kg Japanese quail *(Coturnix coturnix japonica)*	ND	ND

ND – not determined.

3.3.1 Acute /Chronic Toxicity to Fish

Acute toxicity studies in fish have been performed for all three compounds. The 96-hr. LC_{50} values for the acrylamide in nine different species of fish are 100 - 411 mg/l (ABC Labs 1982a, 1982b, and 1982d, Petersen 1985, DOW 1975, Bridie et al., 1979, USTC 1990, Tooby and Hursey 1975, and Woodiwiss and Fretwell 1974). The 96-hr. LC_{50} value for NMA in rainbow trout is approximately 890 ppm (practically non-toxic) while the same value for NBMA is 75 ppm (slightly toxic) (Cooke 1990).

Chronic toxicity of AMD has been characterized in three species of fish. In *Carassiums auratus*, the 7-day LC_{50} and 30-day NOEC were 100 and 50 ppm, respectively (Edwards 1975). In *poecilia reticulata*, the 14-day LC_{50} determined by experimentation and calculation were 2.69 and 5.78 umol/l, respectively (Hermens and Leeuwangh 1982). In rainbow trout, the 15-day EC_{50} was 50 mg/l (Petersen et al., 1987, Petersen and Lech 1987).

3.3.2 Acute/Chronic Toxicity to Aquatic Invertebrates

The acute toxicity of AMD has been tested in three types of aquatic invertebrates. The EC_{50} and NOEC values for daphnia magna are 98 mg/l and 60 mg/l (48 hr.) respectively (ABC, 1982e). In *mysidopsis bahia*, AMD had an LD_{50} of 78 mg/l and NOEC of 5.2 mg/l (96 hr.) while the LC_{50} at 48 hr. was 109 mg/l (EG&G Bionomics 1983). Studies in *mysidopsis bahia* of longer duration demonstrated that the NOEC remained constant out to 28-days (Springborn Bionomics 1985). AMD was tested in *paratanytarsus parthenogenetica* and resulted in 410, 230, and 60 mg/l for the $LC_{50,}$ $EC_{50,}$ and NOEC (48 hr.), respectively. (ABC, 1982c).

The chronic toxicity of AMD has been tested in one of the aquatic invertebrates tested above. In *Mysidopsis bahia*, the 96-hr.and 28-day NOEC was 2.04 mg/l, based upon mortality. The 28-day NOEC, based upon reproduction, was >4.4 mg/l (Springborn Bionomics 1985).

3.3.3 Acute Toxicity to Aquatic Plants

Studies of AMD using *selenastrum capricornutum* demonstrate an inhibitory concentration (IC_{50}) of approximately 70 mg/l (67.7 – 72) (SEPC 1997, Spraggs et al., 1982).

3.3.4 Acute Toxicity to Terrestrial Plants

AMD was tested in the emergence test, root elongation test and germination and growth tests in *impatiens sultanii, brassica rapa* and *lactucua sativa*, respectively. In the emergence test, the NOEC was $\leq$ 2,000 ppm (Bilderback 1981) while the EC_{50} for inhibition of root elongation was 200 ppm (Kuboi and Fuji 1984) In the germination and growth test, inhibition was observed at 5 ppm, but the leachate was not AMD (Hazleton Labs. 1987).

3.3.5 Other

The bioconcentration factors (BCF) for AMD ranges from 0.86 in the carcass to 1.12 in the viscera of Fingerling trout (Petersen et al., 1985). The BCF values of the other two compounds will be similar due to AMD given the fact that their Kow values are similar.

3.3.6 Test Plan for Ecotoxicity

No new ecotoxicity testing is recommended. Acute fish toxicity studies have been performed with all three compounds. The toxic levels of AMD and NBMA are similar while the level for NMA is substantially higher. Additional studies (chronic toxicity to fish and crustacea) are available for AMD.

3.4 Mammalian Toxicity Data

3.4.1 Acute Toxicity

A large number of acute toxicity studies have been performed on the three chemicals under consideration. The results of these studies have been consistent and thus can be easily summarized. Oral LD_{50} values for AMD are consistently in the range of 100 - 200mg/kg for rats (Fullerton et al., 1966; Paulet and Vidal 1974; Tilson and Cabe 1979b; and McCollister et al., 1964), mice (Hashimoto et al., 1981), rabbits (McCollister et al., 1964) and guinea pigs (McCollister et al., 1964). The inhalation LC_{01} values for rats and mice exceed 5.7 ppm since no mortality was observed at the concentration following a 6 hr. nose-only exposure (Friedman, et al., 2001). These values are increased (i.e. the toxicity is decreased) as substitutions occur on the acrylamide moiety. Thus, the oral LD_{50} values for NMA are in the range of 400-677 mg/kg for rats (Batelle, 1981a; Japanese Journal of Hygiene 1979) and mice (Hashimoto et al., 1981; Batelle, 1981b; Cyanamid Report 53-82, 1954) while the rat oral LD_{50} values for NBMA range from 630 – 1,144 mg/kg (Carpenter, 1971; Cytec MSDS No. 4500; RTECS 2001).

The same relationship exists among these compounds with regard to acute dermal toxicity. The LD_{50} values for AMD are 188 and 400 mg/kg for rabbits (Vernon et al., 1990) and rats (Novikova 1979), respectively. The rabbit LD_{50} values for NMA and NBMA are >16,000 (Vernon et al., 1990) and >991 mg/kg (Carpenter 1971), respectively.

The relatively low oral and dermal toxicity of all of these compounds is consistent with the low toxicity of NMA by the inhalation route. The nose-only LC_{50} values for rats, mice and guinea pigs by this route is >39 mg/m^3 (Vernon et al., 1990). As expected, the toxicity for AMD via the inhalation route is somewhat higher than that of NMA; the nose-only LD_{01} for rats and mice is >5.7 ppm (Friedman et al., 2001).

Results of acute toxicity studies with AMD, NMA and NBMA are summarized in Table 5.

Table 5. Results of Acute Toxicity Studies with AMD, NMA, and NBMA

Endpoint	AMD, (CAS # 79-06-1)	NMA, (CAS # 924-42-5)	NBMA, (CAS# 1852-16-0)
Acute oral	Rat, rabbit, mouse, guinea pig LD_{50} = 100-200 mg/kg	Rat, mouse LD_{50} = 400-677mg/kg	Rat LD_{50} = 630 – 1,144 mg/kg
Acute dermal	Rabbit LD_{50} = 188 mg/kg Rat LD_{50} 400 mg/kg	Rabbit LD_{50} >16,000 mg/kg	Rabbit LD_{50} > 991 mg/kg
Acute inhalation	Rat, 6 hr., nose only, LD_{01} > 5.7 ppm Mouse, 6 hr., nose only, LD_{01} > 5.7 ppm	Mice, rats, guinea pigs NOEL >39 mg/m^3	ND

ND = not determined

3.4.2 Repeated Dose Toxicity

A large number of repeated dose studies have been performed with these three compounds. The toxicities (e.g. NOELs) are very similar at comparable dosing-durations and the toxicities increase with increasing dosing durations. Thus, beginning with an AMD monkey study (two doses over two days, i.p.), the NOEL is <100 mg/kg/day (McCollister et al., 1964). For studies with a two to three week duration, the NOEL for AMD is <30 mg/kg/day (i.p. 5x/wk, Jones and Cavanagh 1986) NMA, 50 and 100 mg/kg/day, rat and mouse, respectively (NTP TR-352, 1989), and NBMA 72 mg/kg/day (Huntingdon Research Center 1976). This is the same relationship observed in the acute studies (i.e. AMD being more toxic than the corresponding substituted compounds). The NOELs continue to decrease in four-week studies, where the values for both AMD and NMA are approximately 4 mg/kg/day (AMD: Schulze and Boysen 1991 [rat, gavage], Keefe 1991[rat, drinking water], Satchell 1985 [rabbit]; NMA: Cyanamid Report 53-82). The results of studies having a five to eight week duration demonstrate the absence of adaptation to chronic administration (NOEL of approximately 5 mg/kg/day; Thomann et al., 1974 [dog, capsule], Satchell and McLeod, 1981 [dog, feed] Hersch et al., 1989 [dog, capsule], Maurissen et al 1983 [monkey, drinking water). Three to four month studies in AMD conclude that the NOEL for this dosing period is in the range of 0.2-0.4 mg/kg/day (Burek et al., 1980 [rat, drinking water], Tilson and Cabe 1979a [rat gavage], Eskins et al., 1985 [monkey in juice]). Comparable studies in NMA report a NOEL of 12.5 mg/kg/day in rats and mice (NTP TR 352, 1989).

In long-term studies (1-2 years), monkeys appear to be less sensitive to the toxic effects of AMD than cats which are less sensitive that rats, NOELs of 2.13 – 0.71, 1.0 – 0.3, and 0.1 mg/kg/day, respectively (Johnson et al., 1984 [rat drinking water]; McCollister et al, 1964 [cat and monkey dietary]).

Results of repeated dose toxicity studies with AMD, NMA and NBMA are summarized in Table 6.

Table 6. Results of Repeated Dose Toxicity Studies with AMD, NMA, and NBMA

Endpoint	AMD, (CAS # 79-06-1)	NMA, (CAS # 924-42-5)	NBMA, (CAS# 1852-16-0)
Repeated dose (2 days)	Monkey (i.p.), NOEL <100 mg/kg/day	ND	ND
(16-21 days)	Rat (i.p., 5x/wk), NOEL <30mg/kg/day	Rat, oral NOEL = 50 mg/kg/day Mouse, oral NOEL = 100 mg/kg/day	ND
(28 days)	Rat (drinking water) NOEL = 4.1-4.3 mg/kg/day Rat (gavage), NOEL <10 mg/kg/day Rabbit (s.c, 2x/wk), NOEL <400 mg/4wks.	Rat oral NOEL = 4 mg/kg/day (neurological)	Rat, dietary NOEL=0.062% (≈ 72 mg/kg/day)
(36-56 days)	Dog (capsule), NOEL=5 mg/kg/day Dog (in feed), NOEL <7 mg/kg/day Dog (capsules), NOEL <5.7 mg/kg/day Monkey (drinking water), NOEL <10 mg/kg/day		
(90-120 days)	Rat (drinking water), NOEL = 0.2 mg/kg/day Rat (gavage 3x/wk), NOEL = 5 mg/kg Monkey (in juice, 5x/wk), NOEL <10 mg/kg/day	Rat, (oral) NOEL = 12.5 mg/kg/day Mouse (oral) NOEL = 12.5 mg/kg/day	ND
(1 year)	Monkey (dietary, 5days/wk), NOEL = 1-3 mg/kg/day Cat (dietary), NOEL = 0.3-1.0 mg/kg/day	ND	ND
(2 years)	Rat (drinking water, rat), NOEL = 0.1 mg/kg/day	ND	ND

ND = not determined

3.4.3 Genetic Toxicity

3.4.3.1 In Vitro Testing

Extensive testing of all three compounds provides substantial data of comparability of results. Many Ames tests have been performed and the results for all three compounds are unequivocally negative (AMD: Zeiger et al. 1987; Knaap et al. 1988; Hashimoto and Tanii, 1985; Tsuda et al 1993; NMA: Zeiger, 1988, Hashimoto and Tanii 1985; NBMA: Hazleton Labs. America 1990a). The results from tests of chromosomal aberration are mostly positive in all three compounds (AMD: Tsuda et al 1993, Knapp et al 1988; NMA: Microbiological Assoc. 1986 [negative], NTP Tr-352; 1989 [positive]; NBMA: Hazleton Labs. Amer. 1990b). Other studies performed in AMD vary in their results (AMD: Knaap et al 1988 [kleb. Pneumonia] – negative*;* Vasavada and Padayatty, 1981 [*E. coli* reverse mutation – positive]; Knaap et al 1988 [HPRT mouse lymphoma – positive], Tsuda et al 1993 [HPRT CHO – negative] and Van Horick and Moens 1983, and Miller and McQueen 1986 [UDS – positive and negative, respectively).

Results of in vitro genetic studies with AMD, NMA and NBMA are summarized in Table 7.

Table 7. Results of In Vitro Genetic Toxicity Studies with AMD, NMA, and NBMA

Endpoint	AMD, (CAS # 79-06-1)	NMA, (CAS # 924-42-5)	NBMA, (CAS# 1852-16-0)
Genetic toxicity (in vitro)	Ames tests (w/wo*, multiple tests) – negative Chrom. Abs and SCE (CHO, wo) – positive Bacterial gene mutation assay (Kleb.pneun., wo) – negative E. coli reverse mutation assay (wo) – positive HPRT (mouse lymphoma, w/wo) – positive HPRT (CHO, wo) – negative UDS – positive/negative	Ames test (w/wo, multiple tests) – negative Chrom. Abs and SCE (CHO, w/wo) – positive Chrom. Abs (BALB, w/wo)– negative	Ames test (w/wo, multiple tests) – negative Chrom. Abs (CHO, w/wo) – positive

* with and without metabolic activation
ND = not determined

3.4.3.2 In Vivo Testing

A number of *in vivo* genetic toxicity tests have been performed on AMD and these provide the same distribution of results (i.e. both positive and negative). These include: chromosomal aberrations – negative (Backer et al. 1989) and positive (Shiraishi, 1978; Cihak and Vontorkova, 1988; Adler et al. 1988), sex-linked recessive lethal – negative (Knaap et al. 1988), mouse heritable translocation - positive (Shelby et al. 1987), and rodent dominant lethal – positive (Shelby et al. 1987; Tyl et al, 2000a; Sublet et al. 1989), and negative (Smith et al, 1986), UDS – positive (Sega et al. 1990), micronucleus – positive (Knaap et al 1988), and mouse spot/teratogenicity – positive (Neuhauser-Klaus and Schmahl, 1989), heritable translocations – positive and chromosomal aberrations (Adler et al. 1994) and transgenic mouse tests – negative (Murti et al. 1994; Hoorn et al., 1993). In contrast to AMD, NMA was negative in the micronucleus test (NTP, 1989). It is anticipated that the testing of NBMA would produce results similar to NMA in these types of tests.

Results of in vivo genetic toxicity studies with AMD, NMA and NBMA are summarized in Table 8.

Table 8. Results of In Vivo Genetic Toxicity Studies with AMD, NMA, and NBMA

Endpoint	AMD, (CAS # 79-06-1)	NMA, (CAS # 924-42-5)	NBMA, (CAS# 1852-16-0)
Genetic toxicity (in vivo)	Chrom. Abs.- negative/positive Sex-Linked Recessive Lethal – negative Mouse Heritable Translocation – positive Rodent Dominant Lethal – positive/negative UDS – positive Micronucleus – positive Transgenic Mouse (multiple) – negative	Micronucleus – negative	ND

ND = not determined

3.4.4 Carcinogenicity

Chronic oncogenicity bioassay studies (2 yr.) have been performed in two of the three compounds under discussion. For AMD, a study performed in rats was positive (Johnson et al. 1986). In this study, the majority of the tumors were benign and the authors question their relevance to humans. In addition, AMD was tested in two short term mouse studies, initiation/promotion and lung adenoma, both of which produced positive results and suggested AMD has initiation but not promotional activity (Bull et al. 1984).

Chronic oncogenicity bioassays (2 yr.) have also been performed using NMA. The rat study produced negative results and the mouse study was positive (NTP TR-352, 1989). Thus, the results for both compounds suggest that if these compounds are carcinogens, they are weak ones at worst. Based upon the structural relationships between the compounds in the group, it is likely that the results observed in two of the compounds in this group can be expected in the third compound.

Results of oncogenicity studies with AMD, NMA and NBMA are summarized in Table 9.

Table 9. Results of Carcinogenicity Studies with AMD, NMA, and NBMA

Endpoint	AMD, (CAS # 79-06-1)	NMA, (CAS # 924-42-5)	NBMA, (CAS# 1852-16-0)
Carcinogenicity	Rat, drinking water (0.01 - 2.0 mg/kg/day) – positive Mouse, p.o and i.p (1-60 mg/kg/day) – positive (benign tumors) Mouse, dermal (12,5, 25, 50 mg/kg), – positive with TPA, negative without TPA	Rat (25, 50 mg/kg, 5x/wk) – negative Mouse (25, 50 mg/kg, 5x/wk) - positive	ND

ND = not determined

3.4.5 Reproductive Toxicity

Multiple tests, in two species of animals have been performed on two of the compounds in the chemical class under consideration herein. The results of these studies are clear, neither of the compounds tested produces reproductive effects in the absence of general toxicological effects in the adult. That is, at levels which produce symptoms of general toxicity, reproductive effects *may* be observed (in some cases not). However, reproductive effects are never observed in the absence of general toxicity.

The reproductive studies of AMD include those in which rats (Zenick et al. 1986 [drinking water], Sublet et al. 1989 [gavage], Tyl et al. 2000a [drinking water], Tyl et al. 2000b [gavage], Johnson et al. 1984 [drinking water], and Smith et al. 1986 [drinking water]) and mice (Hashimoto et al. 1981 [gavage], and Sakamoto and Hashimoto, 1986 [drinking water] were evaluated.

Using NMA, three reproductive studies demonstrated the same toxicity pattern (Hashimoto et al. 1981 [gavage], Sakamoto and Hashimoto, 1986 [drinking water], and NTP, 1993 [drinking water. Namely, that these compounds produce reproductive toxicity only as part of a pattern of overall general toxicity. They are not *selective* reproductive toxicants, where the threshold for reproductive effects is observed before other toxic signs can be seen. The consistency of the results in these studies and across the two compounds, taken together with the structural similarity of the compounds, suggests that no additional testing is required to support this class of compounds.

Results of reproductive toxicity studies with AMD, NMA and NBMA are summarized in Table 10.

Table 10. Results of Reproductive Toxicity Studies with AMD, NMA, and NBMA

Endpoint	AMD, (CAS # 79-06-1)	NMA, (CAS # 924-42-5)	NBMA, (CAS# 1852-16-0)
Reproductive toxicity	Rat, one-gen. (drinking water, 4-15 mg/kg/day) positive for reprod. Effects & general tox at the same levels. Rat (gavage, 5-60 mg/kg/day) – positive for reprod. and gen. Effects at the same dose. Rat, two-gen. (drinking water, 0.5-5.0 mg/kg/day) – NOEL=2.0 (prenatal tox.), & 0.5 mg/kg/day (adult tox). Rat, gavage (5-60 mg/kg/day) – reprod. Effects and gen effects at same dose. Rat (drinking water), reprod. and gen. Effects seen at the same level. Rat (drinking water) – pre and post-implant. Loss, not neurotox. obs. Mouse, male only (gavage, 36 mg/kg/day) – positive histopath. Mouse (drinking water, positive – positive for reprod. effects & gen. tox at the same levels.	Mouse (male only, 292 mg/kg/day) – positive on reprod. Organs Mouse 4.3mM in water (0.435 mg/ml) for 6 wks – positive reprod. (male not female) and gen. tox at same levels Mouse, one-gen. (drinking water, 11, 30-40, 115 mg/kg/day) – positive possibly related to dominant lethal effects	ND

ND = not determined

3.4.6 Developmental Toxicity

The potential for chemicals in this group to cause developmental toxicity problems has been addressed by the performance of four studies in three different species of animals. AMD was tested in rats (Edwards, 1976 [dietary], Field et al. 1990 [gavage], Walden et al. 1981 [gavage]), mice (Field et al. 1990 [gavage]) and developing chick embryos (Kankaanpaa et al. 1979 [injection into the egg]). The results of these studies are consistent within themselves and with the results of the reproductive toxicity studies cited above. Specifically, when these compounds induce developmental toxicity, it is only within the context of producing general toxicity. Based upon the structural similarities in this group, the currently available data is sufficient to characterize the overall potential for any member of this group to induce developmental toxicity.

Results of developmental toxicity studies performed using AMD, NMA and NBMA are summarized in Table 11.

Table 11. Results of Developmental Toxicity Studies with AMD, NMA, and NBMA

Endpoint	AMD, (CAS # 79-06-1)	NMA, (CAS # 924-42-5)	NBMA, (CAS# 1852-16-0)
Developmental toxicity	Dev. Chick Embryo (0.007-0.7 mg, day 3) – mortality at 0.7 mg, no malformations Rat (dietary, 15, 30 mg/kg/day, 1-20DG) – minor developmental and gen. tox effects at the same level Rat, gavage (6-20DG, 2.5-15 mg/kg/day) – NOEL = 2.5 (maternal tox), 15 mg/kg/day (developmental) Mouse, gavage (6-17DG, 3 – 45 mg/kg/day) – NOEL = 15 mg/kg/day (both develop and maternal)	ND	ND

ND = not determined

3.4.7 Human Experience

Currently available study results suggest that exposure to AMD is not associated with increased incidence of mortality or tumor formation (Collins et al. 1989; Marsh et al, 1998). However, exposure to AMD does appear to be related to the formation of hemoglobin adducts (Bergmark et al. 1993). Furthermore, it would appear that these adducts may be useful as predictors of AMD induced peripheral neuropathy as technology improves (Calleman et al. 1994).

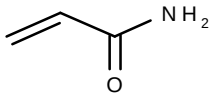
3.4.8 Test Plan for Mammalian Toxicity

The variety and quantity of the studies available and consistency of the study findings across animal species, test paradigms and member of this class of compounds is more than sufficient to characterize the potential mammalian toxicities of concern. Therefore, no additional testing is being proposed.

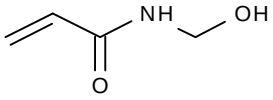
3.5 Conclusion

The NMA/NBMA Association has reviewed the available data and prepared a test plan for two substituted N-(methyl)-acrylamides under the EPA HPV Chemical Challenge Program. These analyses included the evaluation of data related to the SIDS endpoints for environmental fate endpoints, ecotoxicity tests, and human health effects. The existing data evaluated in this analysis included that which is available on the two substituted N-(methyl)-acrylamides (i.e. NMA and NBMA) and that which is available on the very closely related chemical, AMD.

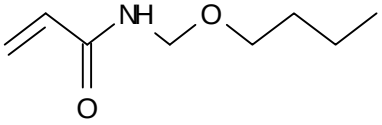
The similarity of these chemicals becomes apparent following a cursory review of their structures. NMA and NBMA are simply AMD with a substitution of a hydrogen atom on AMD molecule. It is known that these three molecules inter-convert.



AMD



NMA



NBMA

The overall conclusions of these analyses include:

1) there exists a very extensive body of studies available on this family of compounds,

2) the chemical and biological characteristics of these compounds are very similar,

3) where differences between these compounds have been detected, the AMD results are the same as or potentially more problematic than the other two (e.g. AMD has a longer environmental $t_{1/2}$, AMD has more toxicity), and

4) the use of data from AMD to substitute for missing data for NMA or NBMA provides a good but likely conservative estimate.

These conclusions are supported in part by the following:

1) The extensive Physical Chemistry information available demonstrates the similarity of these three compounds (e.g. melting and boiling points, vapor pressure). When slight variations are observed, these are reflections of increasing chain length.

2) Sufficient Environmental Fate information is available for each of the three compounds. The similarities in these data are obvious (e.g. all compounds are relatively stable in purified water but all compounds are readily biodegradable by natural occurring microorganisms). In theory, the potential negative environmental impact appears to be greatest with AMD because it has the shortest chain length (i.e. photolysis rate increases with increasing chain length). Thus, the $t_{½}$ for NMA is about 2/3 of that of AMD, while it is only 1/3 of that for NBMA.

3) Consistent with predictions based upon Physical Chemistry and Environmental Fate knowledge, all three compounds are relatively similar with regard to Ecotoxicity. Thus, with regard to acute toxicity in fish, the only category having comparable data on all three compounds, AMD and NBMA have equivalent toxicity while NMA may be somewhat less toxic than the other two. Across a variety of aquatic species, AMD appears to have a relatively steep dose-response curve with both LD_{50} and NOEC levels occurring in the 1 – 100 ppm range.

4) Results of toxicology studies are consistent with the conclusion expressed and supported above (i.e., the compounds are similar but toxicity decreases with chain length). While AMD has a slightly higher toxicity than the other two compounds in this family, the results are reasonably comparable. Thus, acute oral toxicity LD_{50} values for AMD range from 100 – 200 mg/kg for a multiple of animal species. Comparable values for NMA and NBMA are in the range of 400 – 677 and 630 - 1,144 mg/kg, respectively. This exact pattern is observed with even greater clarity when the results of repeated-dose toxicity studies are analyzed.

5) Results of genetic toxicity testing are comparable across the three members of this chemical family. These compounds are negative in the Ames assay, positive in tests of chromosomal aberration and sister chromatid exchange, and mixed when tested using other models.

6) Two of the three compounds (AMD and NMA) have been tested for carcinogenicity and the results are mixed and comparable. AMD produced positive results in rats. In mice, AMD produced positive results by the oral route, but only for benign tumors and mixed results by the dermal route. NMA was found to be positive in mice (by the dermal route) but negative in rats by the oral route.

7) Reproductive testing in AMD and NMA produced equivalent results. AMD may be a reproductive toxicant in male rats, however, the potential effects are confounded by the presence of neurotoxicity.

These data led the NMA/NBMA Association to conclude that the available data is sufficient to meet the requirements for these two substituted N-(methyl)-acrylamides under the EPA HPV Chemical Challenge Program.

4. References

4.1 Acrylamide Dataset References

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